American Chemistry Council

March 7, 2017

Dr. Tina Bahadori
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Dear Dr. Bahadori:

Thank you for meeting with members of the American Chemistry Council (ACC) Formaldehyde Panel on February 21, 2017 to discuss the EPA's Integrated Risk Information System (IRIS) Toxicological Review of Formaldehyde (the "formaldehyde IRIS assessment"). As we discussed, formaldehyde is one of the most studied industrial chemicals in the world. Numerous epidemiology, toxicology, and mechanistic studies have been conducted which improve current understanding of the potential health effects associated with this chemical. These studies have also evaluated both endogenous formaldehyde and the potential contribution of exogenous exposure. After years of study, and hundreds of published scientific papers, recent science continues to strengthen the evidence that formaldehyde is a threshold nasal carcinogen and unlikely to be causally associated with other types of cancers in humans, particularly acute myeloid leukemia (AML).

In contrast to the body of scientific evidence, the EPA's 2010 draft formaldehyde IRIS assessment stated, "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, myeloid leukemia and lymphohematopoietic (LHP) cancers as a group." A 2011 National Academy of Sciences (NAS) peer review was highly critical of EPA's draft formaldehyde IRIS assessment concluding that EPA's assertion that formaldehyde causes leukemia, myeloid leukemia or related hematopoietic cancers was not supported in the draft assessment. Specifically, the NAS committee noted that EPA's conclusion that a causal relationship is supported by the data appeared to be subjective in nature, that no clear scientific framework had been applied by EPA in reaching that conclusion, and further noted inconsistencies in the epidemiologic data, weak animal data and the lack of mechanistic evidence.

In the six years since the NAS report was released, significant new peer reviewed science has been published that further calls into question any causal association between formaldehyde exposure and AML or other lymphohematopoietic malignancies. We consider these studies to be "game-changing" (*i.e.*, critical to the revised formaldehyde IRIS assessment) and they must be reviewed for pertinence and impact on the assessment's conclusions. These studies are summarized in Attachment A, and a few of the studies are also highlighted below:

- A 2015 scientific publication re-examined the underlying data from a seminal epidemiology study that EPA relied on in 2010 and concluded that the underlying data did not demonstrate a statistically significant association between formaldehyde and AML. (Checkoway *et al.,* 2015)

- Recent scientific publications re-evaluated the raw data from the study that was critical in establishing a possible mode of action for leukemia. The results indicated significant methodological limitations (including a failure by the authors to follow the reported protocol), as well as a lack of association between formaldehyde exposure and aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. (Gentry *et al.,* 2014, Albertini *et al.*, 2016 and Mundt *et al.,* 2017)

- Additional epidemiology studies included a follow-up of a large cohort of British industrial workers exposed to formaldehyde that concluded, "Our results provide no support for an increased hazard of myeloid leukemia, nasopharyngeal carcinoma, or other upper airway tumors from formaldehyde exposure." (Coggon *et al.,* 2014)

- A series of published, peer reviewed studies demonstrated conclusively that environmental (or exogenous) formaldehyde that is inhaled or ingested does not reach the bone marrow (where transformations giving rise to leukemia occur). These studies clearly call into question the biological plausibility of a causal connection between exogenous formaldehyde exposure and leukemia. (Lai *et al.*, 2016, Yu *et al.*, 2015, Edrissi *et al.,* 2013, Moeller *et al.*, 2011)

- Two studies conducted by NIH using mice genetically predisposed to leukemias reported no association between formaldehyde exposure and leukemia or endpoints associated with leukemia. (Morgan *et al.*, 2015 and Morgan *et al.*, 2014)

Despite your assurances during the February 21st meeting that the formaldehyde IRIS assessment has been substantially revised to incorporate new scientific evidence generated since 2010 and that all of the NAS recommendations have been addressed and incorporated, we remain concerned that the revised formaldehyde IRIS assessment might not achieve an acceptable level of scientific rigor. We were surprised to learn that the stopping rule for the formaldehyde IRIS assessment already has been invoked at an unspecified date and without due notice to the public. We are disappointed in the continued lack of transparency by the Agency on how and when the stopping rules are applied and the Agency's lack of commitment to using a weight of evidence approach for chemical assessments. As such, ongoing research and research currently undergoing peer review may be arbitrarily and inappropriately excluded from the assessment.

Specifically, the Formaldehyde Panel is concerned that: (a) a transparent, rigorous weight of evidence approach has not been developed or utilized in the formaldehyde IRIS assessment as called for by NAS; (b) programmatic improvements to be adopted for hazard identification and dose-response assessment have not been applied to the formaldehyde IRIS assessment; and (c) the "stopping rules" for formaldehyde have been invoked, without any communication to the public, and that this will preclude the consideration of important new science.

We believe that a revised formaldehyde IRIS assessment that fails to reflect a transparent weight of evidence assessment that fully and critically evaluates and integrates evidence from studies published since the release of the 2010 draft assessment, will not be scientifically robust and may include erroneous conclusions. As the NAS recommended in 2011, a systematic review of all of the studies is needed to support a weight of evidence approach, clearly identifying the highest quality studies and their role in drawing conclusions regarding the causal associations between formaldehyde exposure and health effects. This type of review is necessary to provide transparency surrounding the criteria that have been used to weigh evidence and assess causality in the formaldehyde IRIS assessment. Given that it has been six years since the NAS provided its recommendations, there is no compelling reason why programmatic improvements in systematic review processes cannot also be adopted for formaldehyde. As such, we encourage you to perform a critical systematic review of all the data included in the formaldehyde IRIS assessment, including the research in Attachment A, before any revised formaldehyde IRIS assessment undergoes external review. The new science summarized in Attachment A rises to the level of "game changing" findings and their inclusion and integration into your review is essential.

We trust that as the new EPA NCEA Director you are committed to ensuring that the revised formaldehyde IRIS assessment fully addresses the scientific recommendations identified by the NAS in 2011, both process related and specific to formaldehyde, considering the best available formaldehyde science generated to address those NAS recommendations and integrating all streams of the scientific evidence to reach conclusions regarding formaldehyde's carcinogenicity and toxicity. We hope you will fully consider and address the concerns raised in this letter prior to the release of a revised draft formaldehyde IRIS assessment for public comment and we look forward to opportunities to work constructively with the EPA moving forward.

Sincerely,

Kimberly Wise White, PhD
Senior Director
American Chemistry Council (ACC)
Chemical Products & Technology Division

Cc:
Robert Kavlock

ATTACHMENT A
SUMMARY OF FORMALDEHYDE SCIENCE ADDRESSING NAS RECOMMENDATIONS

NAS (2011) Comment/ Data Gap	**New Evidence**
Epidemiological Evidence	
Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). *(p. 113)*	Conducted additional and refined analysis on the key underlying data (including specifically exposure information which had not been previously provided) utilized in a study relied upon in the draft IRIS assessment (e.g. Zhang *et al*., 2010). Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Additionally, among formaldehyde-exposed workers, no association was observed between individual formaldehyde exposure estimates and frequency of aneuploidy, which the original study authors suggested were indicators of myeloid leukemia risk. *Mundt et al., (2017)*) New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML. *Checkoway et al., (2015)* Associations seen between formaldehyde exposure and Hodgkin leukemia and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. *Checkoway et al., (2015)*
Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. *(p. 113)*	A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoietic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation. *Checkoway et al., (2012)*

Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. *(pp. 112-113)*	Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure. Few deaths occurred within 20+ years of last peak exposure. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (*P*trend= 0.05) and peak (*P*trend = 0.003) exposures. Suggestive associations with peak exposure observed for chronic myeloid leukemia, based on very small numbers. Due to the lack of concordance with other epidemiologic studies and lack of a plausible biological mechanism, the authors considered any causal interpretations of the observed risk patterns to be at most tentative. No other lymphohematopoietic malignancy was associated with either chronic or peak exposure. *Checkoway et al., (2015)*
The selection and use of the NCI cohort (Beane-Freeman et al. 2009) should be further justified. *(p. 112)*	Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941-2012. Results provided no support for an increased hazard of myeloid leukemia from formaldehyde exposure. *Coggon et al., (2014)* Analyzed 15,332 newly diagnosed cases of AML (i.e., not deaths) diagnosed from 1961 to 2005 in Finland, Norway, Sweden, and Iceland, and 76,660 matched controls. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde. *Talibov et al., (2014)* Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases. *Meyers et al., (2013)* Studied occupational risk factors among 671 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy. No increased risk of AML was associated with low exposure to formaldehyde (HR 1.01, 95% CI 0.65 - 1.57) and no AML cases occurred among individuals in the high formaldehyde exposure category. *Saberi et al., (2013)*

Toxicological Evidence	
Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. *(p. 110)*	No cases of leukemia or lymphohematopoietic neoplasia were seen. Formaldehyde inhalation did not cause leukemia in genetically predisposed C3B6.129F1-*Trp53*tm1Brd mice. *Morgan et al., (2014)* Formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. *Morgan et al., (2015)*
Mode of Action Evidence	
Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. *(p. 58)*	Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations. *Schroeter et al., (2014)* With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. *Yu et al., (2015)*
Reconcile divergent statements regarding systemic delivery of formaldehyde *(p.59)*; direct evidence of systemic delivery of formaldehyde is generally lacking. *(p. 5)*	Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. *Yu et al., (2015); Edrissi et al., (2013); Lu et al., (2012); Moeller et al., (2011); Lu et al., (2011)*

Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. *(p. 5)*	Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to formaldehyde alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically not in the bone marrow. Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species– a probable prerequisite for leukemogenesis. *Albertini et al., (2016)* Reanalysis of selected raw data from the Zhang et al. (2010) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by Zhang et al. (2010) raise sufficient questions that limit the use of Zhang et al. (2010) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. *Gentry et al., (2013); Mundt et al., (2017, in press)*
Dose-Response Assessment	
Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. *(p. 14)*	The documentation of the methods applied in the USEPA (2010) IRIS document lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from Beane Freeman et al., (2010). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. *Van Landingham et al., (2016)*
BBDR models developed by Conolly and co-workers should be used. *(p. 58) These* models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. *(p. 57)*	Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand if exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. *Clewell et al., (in preparation)*
Consideration of the use of alternative extrapolation models for the analysis of the cancer data. *(p. 14)*	Results of the "Bottom-up " approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. *Starr and Swenberg, (2013)*

	Updated "Bottom-Up" risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers. *Starr and Swenberg (2016)*
Methods for Evidence Integration	
EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. *(p. 113)*	A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode of action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. *Rhomberg et al., (2011); Rhomberg et al., (2015), Swenberg et al.,(2013)*

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